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Research Article

SYNTHESIS, SPECTRAL CORRELATION STUDY, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SUBSTITUTED 5-(4-FLUOROPHENYL)-3-PHENYLISOXAZOLES

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ABSTRACT

Different substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have been synthesized by condensation of substituted chalcone compounds using the hydroxylamine hydrochloride. The isoxazole compound structures are confirmed by various spectral analyses.These 5-(4-fluorophenyl)-3-phenylisoxazoles have been characterized from the physical constants, UV, FT-IR, ^{1}H and ^{13}C Nuclear magnetic resonance spectral data. The above compound spectral values correlated by using the Hammett constants and Swain's Lupton parameters. The microbial activities of the synthesized isoxazole were evaluated.

Keywords: Substituted 5-(4-fluorophenyl)-3-phenylisoxazole,3-(4-fluorophenyl)-1-phenylprop-2-en-1-one,4-Flurobenzaldehyde, Substituted acetophenones, Correlation study, antibacterial activity, antifungal activity

1. INTRODUCTION

Nitrogen-containing compounds are well known to have a tremendous potential in various fields of organic chemistry. Heterocyclic compounds have wide range of antimicrobial activities [1-4] and medicinal activities, synthetic and natural importance, because they contain hetero atoms like nitrogen, oxygen and sulphur. Heterocyclic compounds like oxazole and isoxazole are extensively used as agrochemical agents and pharmaceutical field. Now days a large population is affected with various diseases because of some fungal species, but very few antifungal drugs are identified for the treatment of fungal infections. The antimicrobial study with quantitative structure activity relationships (QSAR) studies for the drug discovered research are very useful application for medicinal and pharmaceutical field [5]. Isoxazole compounds also have noble effectiveness in thrombosis animal models [6]. In the theoretical heterocyclic chemistry, isoxazole compounds act as decisive part in the development of synthetic organic chemistry [7, 8]. Current paper reports organic synthesis of oxazole and isoxazole compounds followed by base-catalysed condensation method using substituted ketone and benzaldehydes to form the substituted chalcone compounds, which gave corresponding isoxazole derivatives [9-11] using hydroxylamine hydrochloride in alkaline medium. The chalcones are used as main key forerunners in the synthesis of medicinally important aromatic isoxazole compounds. This research work explains the reaction of 4-Fluro benzaldehyde with different substituted acetophenones to form substituted 3-(4-fluorophenyl)-1-phenylprop-2-en-1-ones (Compound-A) in stage-I and substituted compounds (Compound-A) with reaction of hydroxylamine hydrochloride forms 5-(4-fluorophenyl)-3-phenylisoxazole compounds. The various synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazoles structure were confirmed by the tool of elemental analysis study, UV, IR, ^{1}H, ^{13}C nuclear magnetic resonance spectral values. From the literature survey, sufficient evidence not available in this research field of spectral correlation regression analysis of FT-IR, UV and nuclear magnetic resonance of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds. The above spectral values are used to confirm these substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds. In this study, some aryl isoxazoles were synthesized using chalcone compounds using condensation method. Also the effect of substituents has been studied with Hammett equation followed by the study of antimicrobial activities with regard to the synthesized isoxazole derivatives.

2. MATERIALS AND METHODS

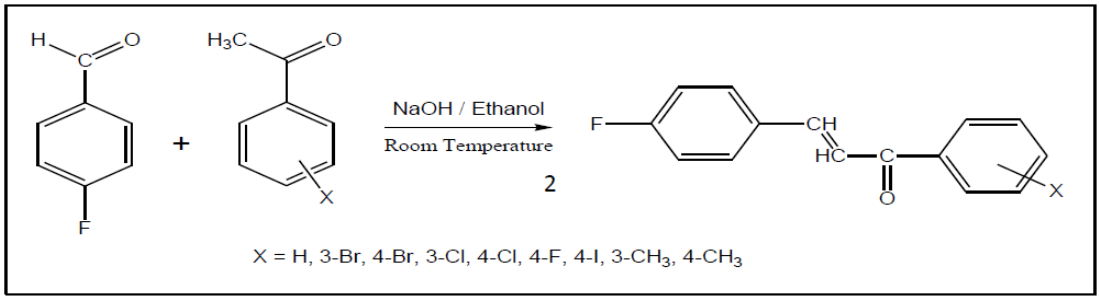
Chemicals were purchased from Aldrich Bangalore. The Suntex melting point instrument was used to check the

melting point of synthesized compounds. UV spectra of substituted oxazoles have been noted using ELICO BL222 Spectrophotometer. Infrared spectra (Potassium bromide) were recorded in AVATAR spectrophotometer. NMR spectra of the synthesized isoxazole compounds were recorded by BURKER spectrometer-500MHz.

2.1. Procedure for preparation of 3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (Stage I)

Appropriate mixture of 4-Fluorobenzaldehyde (100mmol) with *m*- and *p*-substituted acetophenones (100mmol), solution of aqueous NaOH (200 ml 0.5M) and pure ethyl alcohol (Scheme1) were taken in a beaker.

Scheme1: Method of synthesis for substituted 3-(4-fluorophenyl)-1-phenylprop-2-en-1-ones

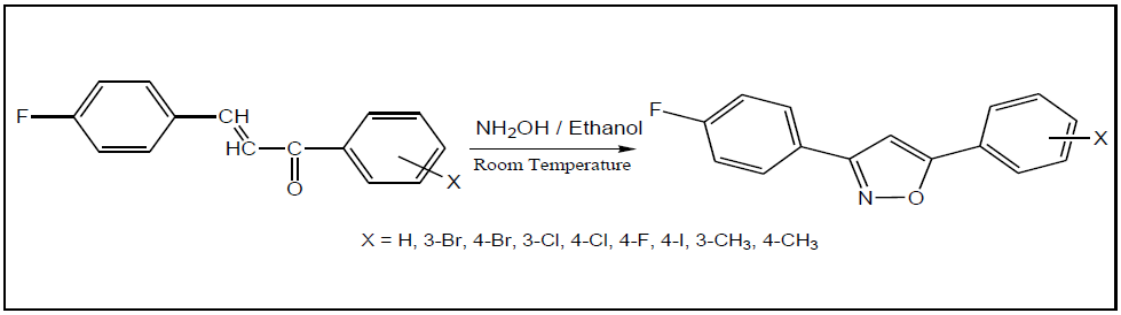


The reaction mixture was stirred vigorously for 30 minutes [12, 13] at 30°C. The conversion of aldehydes was monitored using TLC, then the mixture was allowed in non-disturbed condition for half an hour, then the unreacted reactants were removed with filter paper and washed by using deionized water. Synthesized 3-(4-fluorophenyl)-1-phenylprop-2-en-1-ones were recrystallized with ethyl alcohol. The same procedure was maintained for the substituted 3-(4-fluorophenyl)-1-phenylprop-2-en-1-ones**.**

2.2. Procedure for preparation of 5-(4-fluorophenyl)-3-phenylisoxazole (Stage II)

The synthesized compounds in stage I i.e. 3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (100mmol), hydroxylamine hydrochloride (100mmol) and 0.5 gram sodium hydroxide in 20 mL ethyl alcohol were taken. The contents were condensed for 4 hours [14, 15] (Scheme 2). Completion of the reaction was checked by thin layer chromatography technique. Then, the contents were poured to ice containing water.

Scheme 2: Synthesis of substituted 5-(4-fluorophenyl)-3-phenylisoxazoles



Unreacted reactants, if any, were removed with filter paper and washed using deionized water. 5-(4-fluorophenyl)-3-phenylisoxazoles were recrystallized with ethyl alcohol. The similar procedure was maintained for substituted 5-(4-fluorophenyl)-3-phenylisoxazoles. The synthesized 5-(4-fluorophenyl)-3-phenylisoxazoles were confirmed by physical and spectral data. Physical and Spectral data of above synthesized compounds were as given in Table 1. In the current study the spectral data linearity of synthesized 5-(4-fluorophenyl)-3-phenylisoxazoles have been evaluated with the substituent effect tool. Spectral values for the 5-(4-fluorophenyl)-3-phenylisoxazole, UV max(nm), infrared υC=N,υC=C, υC-H, the ^{1}H of C-H, and the ^{13}C C=N, CH, CH-Ph and C-F values are conformed and given in Table 2.

Table1: Physical constants of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds

Entry	X	Molecular Formula	Molecular Weight	Yield %	Melting Point (^{0}C)	Found (Calcd.) (%) C	H	N
1.	Paren(H)	$C_{15}H_{10}FNO$	239	90	100-101	74.11 (75.30)	4.02 (4.21)	5.10 (5.85)
2.	*m*-Br	$C_{15}H_9FNOBr$	318	92	110-111	56.26 (56.63)	2.08 (2.85)	4.24 (4.40)
3.	*p*-Br	$C_{15}H_9FNOBr$	318	93	150-151	56.28 (56.63)	2.42 (2.85)	4.36 (4.40)
4.	*m*-Cl	$C_{15}H_9FNOCl$	273	89	78-79	65.22 (65.83)	2.98 (3.31)	4.84 (5.12)
5.	*p*-Cl	$C_{15}H_9FNOCl$	273	90	110-111	65.64 (65.83)	3.20 (3.31)	4.98 (5.12)
6.	*p*-F	$C_{15}H_9F_2NO$	257	91	90-91	69.08 (70.04)	3.26 (3.53)	5.24 (5.45)
7.	*p*-I	$C_{15}H_9FNOI$	365	88	120-121	48.26 (49.34)	2.16 (2.48)	3.46 (3.84)
8.	*m*-CH_3	$C_{16}H_{12}FNO$	253	90	140-141	75.64 (75.88)	4.20 (4.78)	5.08 (5.53)
9.	*p*-CH_3	$C_{16}H_{12}FNO$	253	92	145-146	75.76 (75.88)	4.46 (4.78)	5.32 (5.53)

Table 2: The ultraviolet absorption maxima ($\lambda_{max,}$ nm), infrared absoptions (υ, cm^{-1}) and NMR chemical shifts (δ ppm) spectral data of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds

Entry	X	UV	Infra Redυ(cm^{-1})			^{1}H NMR (δ, ppm)		^{13}C NMR (δ, ppm)		
		(nm) λ_{max}	C=N	C=C	C-O-N	C-H	C=N	CH	CH-Ph	C-F
1	H	259.0	1600.41	1507.56	1225.52	6.919	163.27	103.07	167.61	155.39
2	*m*-Br	259.0	1600.00	1503.99	1222.73	6.921	160.92	103.04	164.86	154.93
3	*p*-Br	260.0	1601.16	1508.10	1233.72	6.923	161.53	113.06	166.08	154.98
4	*m*-Cl	272.0	1597.07	1502.35	1225.57	6.922	162.89	103.03	168.36	154.96
5	*p*-Cl	262.0	1598.79	1505.76	1228.88	6.922	161.27	103.07	164.33	154.94
6	*p*-F	271.0	1599.48	1500.07	1219.19	6.922	162.59	113.54	168.63	154.36
7	*p*-I	269.0	1599.65	1498.97	1229.50	6.923	163.23	110.06	167.23	155.36
8	*m*-CH_3	262.0	1601.17	1513.20	1223.69	6.996	163.87	103.07	168.15	155.04
9	*p*-CH_3	262.0	1600.10	1508.67	1222.53	6.920	161.16	103.04	164.91	154.94

3. RESULTS AND DISCUSSION

3.1. Spectral linearity of 5-(4-fluorophenyl)-3-phenylisoxazoles

In this study, substituent effects of synthesized 5-(4-fluorophenyl)-3-phenylisoxazole compounds were evaluated by spectral linearity method. The detected spectral values of 5-(4-fluorophenyl)-3-phenylisoxazoles, UV λmax (nm), infrared(cm^{-1}) υC=N, υC=C, υCON, the ^{1}H C-H and ^{13}C C=N, CH, CH-phenyl, C-F are regression analysis was done with substituent Hammett values [16-20].

3.1.1. UV spectral study

Measured absorption maxima (λ_{max} nm) values of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds had been recorded, and presented in Table 2. Using single and multi-linear regression analysis [16-20] for above spectral data are correlated with Hammett substituent constants and *F* and *R* parameters. The statistical analyses values are presented in Table 3.

Hammett equation used for the correlation analysis, involving the absorption maxima is as shown below in equation (1).

$$\lambda = \rho\sigma + \lambda o \quad \ldots(1)$$

where, λ_o is the frequency for the parent member of the series.

From the Table 3, UV (λ_{max}nm) data of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds, have shown poor correlations ($r < 0.900$) with Hammett substituent constants and *F* and *R* parameters. For the reason, the weak polar, inductive, field and resonance effects of substituents for predicting the reactivity through resonance of the UV absorption as per conjugative structure as shown in Fig.1.

Except those with σ_R and *R* parameter, positive ρ values were received from all the correlations. From the positive ρ value, the common substituent effect operated in UV in substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

Table 3: The results of statistical analysis of ultraviolet absorption maxima ($\lambda_{max,}$ *nm)*, infrared absoptions *(υ, cm^{-1})* and NMR chemical shifts (δ ppm) of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constants σ, σ^+, σ_I, σ_R and *F* and *R* parameters.

Freq	Cons	r	I	ρ	s	n	Correlated derivatives
λ_{max}	σ	0.718	263.34	4.850	5.46	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.819	263.93	1.432	5.52	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.843	261.32	8.896	5.01	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.864	259.77	-25.504	4.25	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.853	250.53	10.680	4.70	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.858	259.64	-19.391	4.49	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
υ(cm^{-1}) C=N	σ	0.905	1600.20	-3.304	1.17	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.904	1599.82	-1.494	1.22	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.904	1600.46	-2.350	1.19	8	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.903	1600.25	3.000	1.28	8	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.903	1600.38	-1.930	1.24	8	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.901	1599.99	1.069	1.34	8	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
υ(cm^{-1}) C=C	σ	0.905	1507.01	-11.976	4.17	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.905	1505.73	-7.089	4.00	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.907	1509.35	-13.123	3.33	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.906	1508.90	21.114	3.84	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.907	1509.72	-13.291	3.16	8	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *m*-CH_3, *p*-CH_3
	R	0.905	1508.79	15.107	4.13	7	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-CH_3
υ(cm^{-1}) C-O-N	σ	0.903	1224.66	7.732	4.41	6	Parent(H), *p*-Br, *p*-Cl, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.904	1225.44	5.438	4.20	8	Parent(H), *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.902	1224.51	3.961	4.57	7	Parent(H), *m*-Br, *m*-Cl, *p*-Cl, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.903	1227.77	12.532	4.35	8	Parent(H), *m*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.801	1225.53	0.506	4.69	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.901	1228.24	11.325	4.28	8	Parent(H), *m*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
δ C-H (ppm)	σ	0.903	6.936	-0.047	0.02	8	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *p*-CH_3
	σ^+	0.907	6.932	-0.049	0.01	8	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3
	σ_I	0.904	6.944	-0.048	0.02	8	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *p*-CH_3
	σ_R	0.821	6.936	0.041	0.02	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.841	6.942	-0.040	0.02	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.802	6.932	0.012	0.02	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
δ C=N (ppm)	σ	0.902	162.51	-1.545	1.12	7	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3
	σ^+	0.904	162.36	-1.275	1.06	7	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3
	σ_I	0.833	162.73	-1.438	1.10	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.802	162.44	0.860	1.16	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.822	162.63	-1.033	1.13	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.822	162.40	0.448	1.16	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
δ C-H (ppm)	σ	0.806	105.89	1.619	4.99	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.822	105.97	2.890	4.87	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.904	103.19	9.666	4.27	6	Parent(H), *p*-Br, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.963	102.38	-22.522	3.87	8	Parent(H), *m*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.961	102.30	11.737	3.80	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.961	101.57	-20.195	3.67	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
δ CH-Ph (ppm)	σ	0.913	166.83	-1.129	1.76	7	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3
	σ^+	0.902	166.73	-1.012	1.74	7	Parent(H), *m*-Br, *p*-Br, *p*-Cl, *p*-F, *p*-I, *m*-CH_3
	σ_I	0.805	166.79	-0.371	1.78	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.820	166.13	-3.318	1.72	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.800	166.50	0.537	1.77	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.821	166.02	-2.925	1.71	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
δ C-F (ppm)	σ	0.850	154.99	-0.042	0.31	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ^+	0.803	154.98	0.031	0.31	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_I	0.842	155.14	-0.513	0.28	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	σ_R	0.985	155.31	1.946	0.16	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	F	0.960	155.21	-0.697	0.25	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3
	R	0.984	155.34	1.603	0.16	9	Parent(H), *m*-Br, *p*-Br, *m*-Cl, *p*-Cl, *p*-F, *p*-I, *m*-CH_3, *p*-CH_3

r = Correlation co-efficient; ρ = slope; I = Intercept; s = Standard deviation; n = Number of substituents

For single parameter study all the correlations failed for the UV absorption maximum (λ_{max}nm) values with various Hammett substituent constants and *F* and *R* parameters, it was decided to confirm with the multi correlation [21] analysis. But satisfactory correlations values were obtained from the multi correlation analysis like (2) and (3).

$$\lambda max(nm)=259.75\ (\pm 2.678) + 0.292(\pm 8.556)\sigma_I - 25.137(\pm 16.385)\sigma_R \quad \ldots(2)$$

(r = 0.964, n = 9, *P*> 90%)

$\lambda max(nm)=259.48(\pm 2.931) + 3.909(\pm 10.292)F - 14.444(\pm 16.912)R$ ...(3)
(r = 0.960, n = 9, *P*> 90%)

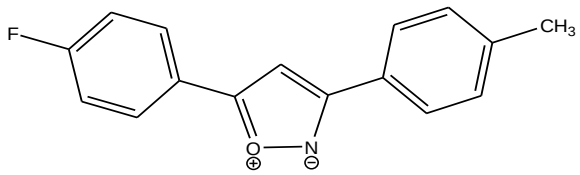


Fig. 1: conjugative structure of 5-(4-fluorophenyl)-3-phenylisoxazole

3.1.2. IR spectral study of 5-(4-fluorophenyl)-3-phenylisoxazole compounds

The IR of υC=N, υC=C, υC-O-N of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compound values are show in Table 2.

Using single and multi-linear regression analysis [16-20] for above infrared frequency spectral values are correlated with Hammett substituent constants and *F* and *R* parameters. The statistical analyses values are presented in Table 3. The correlation analysis for IR, Hammett equation used in the form of equation (4).

$\upsilon = \rho\sigma + \upsilon_o$ ...(4)

Here υ_o parent member for the series.

3.1.2.1. IR spectral regression for υC=N

In the Table 3, IR data C=N of the compound 5-(4-fluorophenyl)-3-phenylisoxazoles with Hammett constants σ(r=0.905) and σ^+(r=0.904) have shown satisfactory correlations. Except *m*-Cl substituent the IR C=N values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constants σ_I(0.904) σ_R(0.903) and *F* (0.903) and *R* (0.901) parameters showed satisfactory correlations.

All the correlations displayed negative ρ values except σ_R constant and *R* parameter. This shows that reverse substituent effect operate to respect IR frequency C=N values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

3.1.2.2. IR spectral regression for υC=C

In the Table 3, IR data C=C of the compound the 5-(4-fluorophenyl)-3-phenylisoxazoles with Hammett constants σ (0.905), σ^+(0.905), σ_I (0.907) and σ_R (0.906) have shown satisfactory correlations.

Except *p*-I substituent the IR C=C values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with *F* (0.907) parameter have shown satisfactory correlation. Except *p*-I and *m*-CH_3 substituents the IR C=C values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with *R* (0.905) parameter have shown satisfactory correlation.

All the correlations have shown negative ρ values except σ_R constant and *R* parameter. This shows that reverse substituent effect operate to respect IR frequency C=C values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

3.1.2.3. IR spectral regression for υC-O-N

In the Table 3, IR data C-O-N of the compounds except *m*-Br, *m*-Cl and *p*-F of 5-(4-fluorophenyl)-3-phenylisoxazoles with Hammett substituent constant σ (0.903) has shown satisfactory correlation. Except *m*-Br substituent the IR C-O-N values of 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constant σ^+(0.903) have shown satisfactory correlation. Except *p*-Br and *p*-F substituents the IR C-O-N values of 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constant σ_I (0.902) have shown satisfactory correlation. Except 4-Br substituent the IR C-O-N values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constant σ_R (0.903) and *R* (r=0.901) parameter have shown satisfactory correlations. Positive ρ values were received from the all correlations. This shows that normal substituent effect operate to respect IR frequency C-O-N values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

Since some of the single parameter correlations are failed for the infrared frequencies (cm^{-1}) of υC=N, υC=C, υC-O-N values with various Hammett substituent constants and *F* and *R* parameters, it was decided to confirm with the multi correlation [21] analysis. But satisfactory correlations values were obtained from the multi correlation analysis like (5) to (10).

$\upsilon C{=}N(cm^{-1}) = 1600.47(\pm 0.753) - 2.330(\pm 2.407)\sigma_I + 0.075(\pm 4.610)\sigma_R$ ...(5)
(0.904, n = 9, *P*> 90%)

$\upsilon C{=}N(cm^{-1}) = 1600.14(\pm 0.784) - 3.513(\pm 2.754)F - 3.376(\pm 4.526)R$ ...(6)
(0.904, n = 9, *P*> 90%)

$\upsilon C{=}C(cm^{-1}) = 1509.86(\pm 2.029) - 10.337(\pm 6.480)\sigma_I + 8.138(\pm 12.411)\sigma_R$ ...(7)
(0.907 n = 9, *P*> 90%)

$\upsilon C{=}C(cm^{-1}) = 1509.41(\pm 2.067) - 15.268(\pm 7.260)\ F - 4.217(\pm 11.930)R$ ...(8)
(0.907, n = 9, *P*> 90%)

$\upsilon C\text{-}O\text{-}N(cm^{-1}) = 1226.42(\pm 2.026) + 14.466(\pm 6.472)\sigma_I + 30.691(\pm 12.394)\sigma_R$ ...(9)
(0.907, n = 9, *P*> 90%)

$\upsilon C\text{-}O\text{-}N(cm^{-1}) = 1227.66(\pm 2.290) + 14.298(\pm 8.041)F + 29.421(\pm 13.213)R$ ...(10)
(0.970, n = 9, *P*> 95%)

3.1.3. NMR spectral study of 5-(4-fluorophenyl)-3-phenylisoxazole compounds

^1H and ^{13}C NMR spectral values, have been found in correlation with Hammett equation [16-20] as per the equation (11)

$\delta = \rho\sigma + \delta_o$ ...(11)

Here δ_o parent member for the series.

3.1.3.1. ^1H NMR Spectral regression of C-H

As presented in the Table 3, ^1H NMR data C-H of the compounds except *m*-CH_3, of 5-(4-fluorophenyl)-3-phenylisoxazoles with Hammett constants σ (0.903) and σ_I (0.904) has shown satisfactory correlations. ^1H NMR data C-H of the compounds except *p*-CH_3, of all 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constant σ^+(0.907) have shown satisfactory correlation. However, C-H ^1H NMR of 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constant σ_R and *F* and *R* have shown poor correlations ($r < 0.900$). The conjugative structure in Fig. 1 shows the weak field and resonance effects act as reactivity, it is reason for the poor correlations. The negative ρ values received from all the correlations. This showed that reverse substituent effect operate to respect ^1H NMR values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds. Since some of the single parameter correlations failed to ^1H NMR chemical shifts (δ ppm) values with various Hammett substituent constants and *F* and *R* parameters, it is decided to confirm with the multi correlation [21] analysis. But satisfactory correlations values were obtained from the multi correlation analysis like (12) to (13).

$\delta C\text{-}H(ppm) = 6.942(\pm 0.014) - 0.059(\pm 0.046)\sigma_I - 0.032(\pm 0.088)\sigma_R$ ...(12)
(0.950, n = 9, *P*> 95%)

$\delta C\text{-}H(ppm) = 6.936(\pm 0.014) - 0.084(\pm 0.050)F - 0.094(\pm 0.083)R$ ...(13)
(0.956, n = 9, *P*> 95%)

3.1.3.2. ^{13}C NMR regression of 5-(4-fluorophenyl)-3-phenylisoxazole compounds

3.1.2.2.1. ^{13}C NMR regression of C=N (ppm)

From the Table 3, the assigned C=N ^{13}C NMR chemical shifts (δ ppm) values except 3-Cl and 4-CH_3 of substituents of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constants σ(r=0.902) and σ^+(r=0.904) have shown satisfactory correlations. However, C=N ^{13}C NMR chemical shifts(δ ppm) values of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constant σ_I, σ_R and *F* and *R* parameters have shown poor correlations ($r < 0.900$).

This is reason for weak inductive, field and resonance effects of substituents predicting the reactivity on the chemical shifts through resonance as per the conjugative structure as shown in Fig 1. All the correlation showed negative ρ values except σ_R and *R* parameter. This shows that reverse substituent effect operate to respect ^{13}C NMR chemical shifts(δ, ppm) values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

3. 1. 3. 2. 2.^{13}C NMR Spectral regression of C-H (ppm)

From the Table3, the assigned C-H ^{13}C NMR chemical shifts(δ ppm) values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with *F* (r=0.961) and *R* (r=0.961) parameters have shown satisfactory correlations. Except 3-Br, 3-Cl and 4-Cl substituents of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constant σ_I(r=0.904) have shown satisfactory correlations. Except 4-Br substituent the C-H ^{13}C NMR chemical shifts (δ ppm) values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constant σ_R(r=0.963) have shown satisfactory correlation. However, C-H ^{13}C NMR chemical shifts (δ ppm) values of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constants σ and σ^+ have shown poor correlations ($r < 0.900$). This is reason for weak polar effect of substituents predicting the reactivity on the chemical shifts through resonance as per the conjugative structure as shown in Fig 1. All the correlations have shown positive ρ values. This is show the reverse substituent

effect operate to respect ^{13}C NMR chemical shifts(δ ppm) values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

3. 1. 3. 2. 3.^{13}C NMR Spectral regression of CH-Ph (ppm)

From the Table 3, the assigned CH-Ph ^{13}C NMR chemical shifts (δ ppm) values except 3-Cl and 4-CH_3 of substituents of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constants σ(r=0.913) andσ^+(r=0.902) have shown satisfactory correlations. However, CH-Ph ^{13}C NMR chemical shifts(δ ppm) values of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constant σ_I, σ_R and *F* and *R* parameters have shown poor correlations (r < 0.900). This is reason for weak inductive, field and resonance effects of substituents predicting the reactivity on the chemical shifts through resonance as per the conjugative structure as shown in Fig 1. All the correlations have shown negative ρ values except *F* parameter. This shows that reverse substituent effect operate to respect ^{13}C NMR chemical shifts (δ ppm) values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

3. 1.3.2. 4.^{13}C NMR Spectral regression of C-F (ppm)

As stated in the Table 3, the assigned C-F ^{13}C NMR chemical shifts (δ ppm) values of all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett constants σ_R (r=0.985) and *F* (r=0.960) and *R* (r=0.984) parameters have shown satisfactory correlations. However, C-F ^{13}C NMR chemical shifts(δ ppm) values of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds with Hammett substituent constants σ, σ^+ and σ_I have shown poor correlations (r < 0.900). This is reason for weak polar and inductive effects of substituents predicting the reactivity on the chemical shifts through resonance as per the conjugative structure as shown in Fig 1. All the correlations have shown positive ρ values except σ and σ_I and *F* parameter. This is show the reverse substituent effect operate to respect ^{13}C NMR chemical shifts(δ ppm) values in all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds.

Since some of the single parameter correlations failed to ^{13}C NMR chemical shifts (δ ppm) values with Hammett constants and *F* and *R* parameters, it was decided to go with multi regression analysis with Swain-Lupton's [21] parameters. But the multi regression analysis gave satisfactory correlations as shown in the following equations (14) to (21).

$$\delta C{=}N(ppm){=}162.633(\pm0.686){-}2.006(\pm2.192)\sigma_I{-}1.657(\pm4.179)\sigma_R \quad \ldots(14)$$
(r = 0.932, n = 9, *P*> 90%)

$$\delta C{=}N(ppm){=}162.485(\pm0.732){-}2.024(\pm2.571)F{-}2.114(\pm4.225)R \quad \ldots(15)$$
(r = 0.933, n = 9, *P*> 90%)

$$\delta C\text{-}H(ppm){=}102.060(\pm2.405){+}3.431(\pm7.683)\sigma_I{-}18.214(\pm14.714)\sigma_R \quad \ldots(16)$$
(r = 0.964, n = 9, *P*> 95%)

$$\delta C\text{-}H(ppm){=}101.350(\pm2.334){+}5.580(\pm8.195)F{-}13.132(\pm13.466)R \quad \ldots(17)$$
(r = 0.970, n = 9, *P*> 95%)

$$\delta CH\text{-}Ph(ppm) {=}166.381(\pm1.031){-}2.642(\pm3.295)\sigma_I{-}6.634(\pm6.310)\sigma_R \quad \ldots(18)$$
(r = 0.930, n = 9, *P*> 90%)

$$\delta CH\text{-}Ph(ppm){=}166.110(\pm1.105){-}2.049(\pm3.883)F{-}5.519(\pm6.380)R \quad \ldots(19)$$
(r = 0.934, n = 9, *P*> 90%)

$$\delta C\text{-}F(ppm){=}155.286\ (\pm0.096) + 0.267\ (\pm0.307)\ \sigma_I{+}2.282\ (\pm0.589)\sigma_R \quad \ldots(20)$$
(r = 0.987, n = 9, *P*> 95%)

$$\delta C\text{-}F\ (ppm) {=}155.343\ (\pm0.109){+}\ 0.134(\pm0.384)\ F{+}1.773(\pm0.631)R \quad \ldots(21)$$
(r = 0.985, n = 9, *P*> 95%)

3.2. Anti-microbial activities of 5-(4-fluoro phenyl) -3- phenylisoxazole compounds

The substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have extensive variety of biological activities these multi-prolonged activities, because they have different substituents and the unsaturation of C=N, C=C, -C-O-N- moiety in the heterocyclic ring. Generally isoxazole compounds and their derivatives possess antibacterial [22], antifungal [23], anti-inflammatory [24], anti-viral [25], anticonvulsant [26], antitumor [27], analgesic [28] and hemotherapy [29] activities. The isoxazole ring contain penicillin compounds act as effective antibacterial agent [30]. Hence, it was planned to study their antimicrobial activities against respective gram positive and gram negative bacterial strains and fungal species.

3.2.1. Antibacterial study

Antibacterial study was performed by using disc diffusion method [31]. About 0.5 ml test bacterial sample was spreaded uniformly on the solidified Mueller Hinton agar using sterile glass spreader for each Petri plate. Whatmann No.1 filter papers of 5mm diameter were prepared and impregnated to 5-(4-fluorophenyl)-3-phenylisoxazole compounds then placed to medium with the help of sterile forceps. To avoid collection of water droplets over the medium, the plates were kept upside down at 37°C in incubator for 24 hours. The plates were visually examined after 24 hours and the diameter of the zone of inhibition values were measured. The same procedure was repeated for triplicate results. The antibacterial screening effect of synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds are shown in Fig 2 (Plates 1-20).

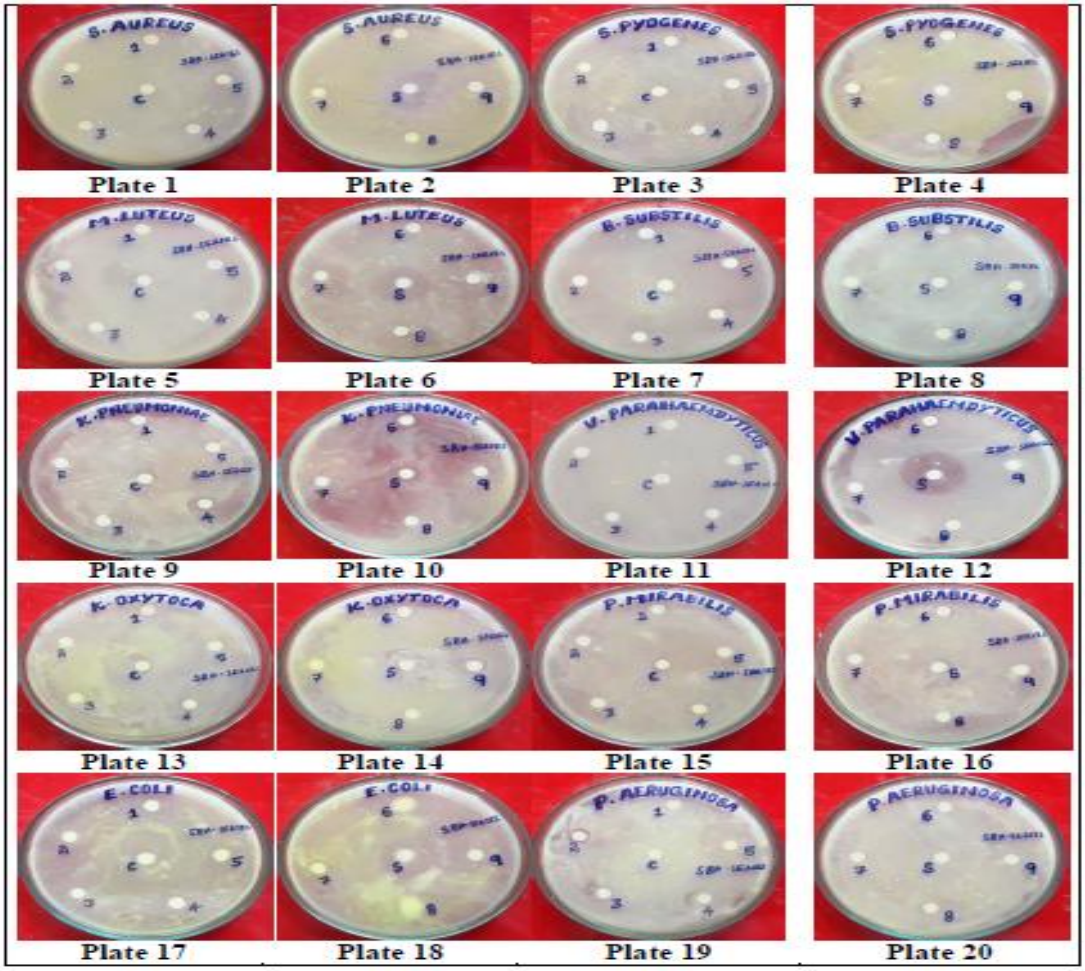


Fig. 2: Antibacterial activities of Substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds

All the synthesized isoxazole were studied for the antibacterial activities against four gram positive pathogenic strains *S. Aureus, S. Pyogenes, M. Luteus, B. Substilis and* six gram negative strains *K. Pneumoniae, V.Parahaemdyticus, K. Oxytoca, P. Mirabilis, E. Coli, P. Aeruginosa*. The Ciprofloxacin was taken as the standard compound and disc diffusion technique was followed at a concentration of 250µg/mL.

Table 4 shows the zone of inhibition values and Fig. 3 shows the corresponding clustered column chart. In general all the substituents possessed a good antibacterial activity against the all the microorganisms. The satisfactory antibacterial activities were showed by all the substituents except 4-Iodo and 3-methyl substituents. A good antibacterial activity was recorded for 4-bromo substituent against *B. Substilis bacterial strain*. A good antibacterial activity was observed for 4-methyl substituent against *K. Oxytoca bacterial strain*. The 3-bromo and 3-chloro substituents possessed antibacterial activities against *P. Aeruginosa bacterial* strain. The 4-iodo substituent has good antibacterial activity against *P. Mirabilis* bacterial strain.

Table 4: Antibacterial activity of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds

			(Zone of inhibition(mm) values)								
			Gram +Ve bacteria					*Gram –Ve bacteria*			
Entry	X	*S1*	*S2*	*S3*	*S4*	*S5*	*S6*	*S7*	*S8*	*S9*	*S10*
1	H	6	7	6	6	7	6	6	6	6	6
2	*m*-Br	6	7	6	6	6	6	6	6	6	8
3	*p*-Br	6	7	6	8	6	6	7	6	6	6
4	*m*-Cl	6	6	6	6	8	7	6	7	8	8
5	*p*-Cl	7	6	6	6	6	6	6	6	7	7
6	*p*-F	6	7	7	6	7	6	6	6	7	6
7	*p*-I	6	8	6	6	6	7	6	8	7	-
8	*m*-CH_3	-	6	7	-	6	6	6	7	6	6
9	*p*-CH_3	6	6	7	6	7	7	8	7	6	6
Standard	Ciprofloxacin	7	9	9	7	9	10	7	8	10	7
Control	DMSO	0	0	0	0	0	0	0	0	0	0

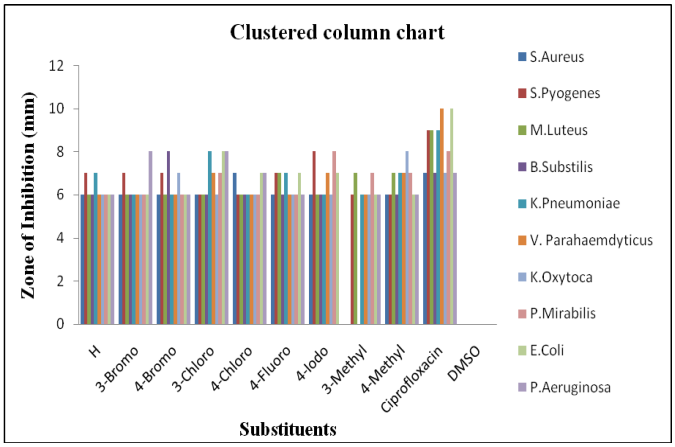


Fig. 3: Antibacterial activities of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds -clustered column chart

3.2.2. Antifungal study

The disc diffusion technique [31] was used for antifungal study. The PDA medium was prepared and sterilized for above procedure. The Petri-plates were filled with 1ml of the fungal species followed by PDA medium (ear bearing heating condition). The synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds had been studied for anti-fungal activities against three fungal species namely *A. niger, M. specie,* and *T. viride.* For uniform spreading of the species in the plates rotated clockwise and counter clock-wise. About 15mg of isoxazole compounds dissolved in 1mL of DMSO solvent (for prepare test solution) and discs were impregnated. Plates were kept for 24 hours for medium allow solidifying. The plates were visually examined and measured the diameter for the zone of inhibition values. The same procedure was repeated for triplicate results. Antifungal activities of synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds are shown in Fig. 4 for Plates (21-26), the zone of inhibition values are shown in Table 5 and the clustered column chart, shown in Fig. 5.

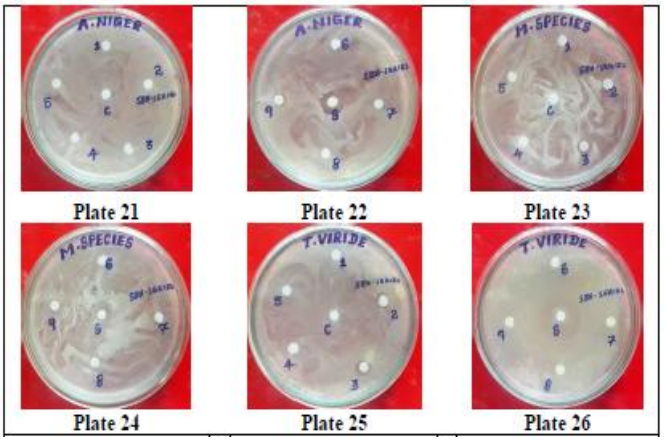


Fig. 4: Antifungal activities of substituted 5-(4-fluorophenyl)-3-phenylisoxazoles.

Table 5: Antifungal activities of substituted 5-(4-fluorophenyl)-3-phenylisoxazoles

		(Zone of inhibition(mm) values		
Entry	X	*A.niger*	*M.species*	*T.viride*
1	H	6	6	6
2	*m*-Br	6	6	7
3	*p*-Br	-	8	7
4	*m*-Cl	6	7	-
5	*p*-Cl	6	6	6
6	*p*-F	6	-	6
7	*p*-I	6	6	6
8	*m*-CH_3	-	6	6
9	*p*-CH_3	7	6	6
Standard	Miconazole	11	10	12
Control	DMSO	0	0	0

All substituents have satisfactory antifungal activities except 4-bromo, 3-chloro, 4-fluoro and 3-methyl substituents. It reveals that the compounds with 4-Br substituents have good antifungal activity against *M. species* fungal species. Except 4-fluoro substituent, all substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have antifungal activities against *M.species*

fungal species. Except 3-chloro substituent, all the substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have antifungal activities against *T.viride* fungal species.

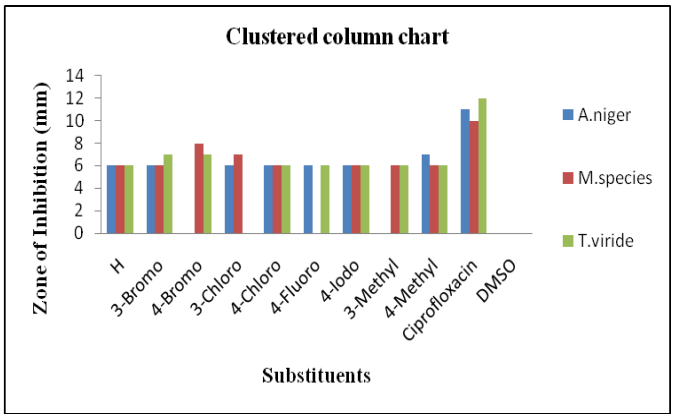


Fig. 5: Antifungal activities of substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds-clustered column chart

4. CONCLUSIONS

The present research work involves synthesis for substituted 3-(4-fluorophenyl)-1-phenylprop-2-en-1-one in stage-I from 4-fluoro benzaldehyde and substituted acetophenones compounds with the help of condensation method. In stage-II substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds synthesized from stage-I 3-(4-fluorophenyl)-1-phenylprop-2-en-1-one compound and hydroxylamine hydrochloride by 4 hour condensation. These synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have been characterized with the physical constants, spectral data. The UV, FT-IR, proton NMR and carbon-13 Nuclear Magnetic Resonance spectral values of these isoxazole compounds have been correlated with the Hammett constants and *F* and *R* parameters. From the statistical analyses results the effects of substituent for the spectral data have been studied. Few numbers of satisfactory correlations were obtained from single parameter regression analyses for spectral correlations study with Hammett substituents constants and Swain-Lupton's parameters. But, the multi-regression analyses have shown satisfactory correlations. All the synthesized substituted 5-(4-fluorophenyl)-3-phenylisoxazole compounds have been studied antimicrobial activities using Bauer-Kirby method. Good and satisfactory antibacterial and antifungal activity was observed by all the substituents against microorganisms except few cases.

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